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THE VALUE OF CIRCULATION TIMES

Circulation time is the measured interval during which the fastest signal-bearing portion of an injected substance travels the shortest path through the circulatory system to reach a designated site where it produces its characteristic physiologic or physical response. Notwithstanding theoretic objections, circulation times are of value clinically because of the narrow range of circulation times in health and the characteristic alterations in disease.

Early methods which led to pioneer observations on the velocity of blood flow in man were almost entirely objective, for instance, radium emanation (the apparatus precludes its general application), histamine (the facial flush may be accompanied by dyspnea and violent headache) and sodium cyanide (the sudden deepening of respiration may be masked by cardiac dyspnea). Only the fluorescein method as recently modified by the use of ultraviolet irradiation has found wide practical application. Papaverine hydrochloride (the end-point is a sudden deep inspiration), radioactive sodium (its detection requires a Geiger Müller counter), and the photoelectric cell-methylene blue methods have limited clinical applicability.

Alpha-lobeline effects an end-point characterized by coughing and choking, and yields circulation times from 25 to 40 per cent lower than those obtained by other methods. Alpha-lobeline is unsuitable for studying circulation speed because it is a pharmacologically active alkaloid with an unclear seat of action and unpleasant side reactions.

Similar short circulation times have been obtained by Sussman who has been employing concentrated diodrast for contrast visualization of the heart and great vessels. Because of the abbreviated roentgen times which may be due in part to the elimination of the reaction time proper, the question has been raised whether the values obtained with other physical or biochemical methods really represent the true velocity of blood flow, and whether the reaction time of such methods may be a considerable fraction of total circulation time.

Subjective methods have recently come into wider use. Use of calcium chloride, magnesium sulfate, calcium gluconate, and a mixture of magnesium sulfate, calcium gluconate, sodium chloride and copper sulfate for the estimation of blood flow in various parts of the body has yielded uniform results. By these methods, the circulation time from the arm to the tongue, from the arm to each hand and to each foot (as in the study of peripheral vascular disease) can be roughly determined.

Of all substances employed for the purpose decholin (5 cc. to a 20 per cent solution of sodium dehydrocholate) seems preferable. It produces a bitter taste which passes rapidly from the base to the tip of the tongue and rapidly diminishes. The decholin arm-to-tongue time ranges between 10 and 16 seconds.

Calcium gluconate (4 cc. of a 20 per cent solution) which is the most reliable of the many substances producing a wave of heat as the end-point, must be used cautiously in digitalized subjects because of the possibility of a calcium-digitalis synergistic effect on the myocardium. The calcium gluconate arm-to-tongue time ranges between 10 and 18 seconds.

Saccharin (2.5 gm. of soluble saccharin dissolved by heating in 2.5 cc. of water and allowed to cool to room temperature) yields a sweet taste in the throat, which passes rapidly from the base to the tip of the tongue and quickly vanishes. The saccharin arm-to-tongue time ranges between 9 and 16 seconds.

Circulation times obtained with sodium fluorescein (2 c.c. of a 20 per cent solution) are nearly identical with those just mentioned. Whereas the decholin, saccharin, and calcium measure the arm-to-tongue time, fluorescein measures the arm-to-lip or conjunctiva time, depending upon which site is chosen for the registration of the end-point. The excellent objective method requires a darkened room as well as a source of ultraviolet light (for example: an argon glow lamp with a heat resisting purple filter). A recent modification employing a histamine wheal permits sharper visualization of the fluorescent end-point. The appearance of the brilliant greenish yellow fluorescence in the skin at sites prepared with histamine has been effectively employed in the study of peripheral vascular disease.

Attempts have been made in recent years to study the circulation time in segments of the circulatory pathway through the lungs. Blumgart and Weiss were the first to measure by means of radium emanation the "arm-to-right heart" time and the "pulmonary circulation" time. Robb and Weiss employed sodium cyanide to measure "peripheral circulation" time and "crude pulmonary" time. Hitzig introduced ether (5 minims mixed with 10 minims of saline solution), a volatile substance which boils at body temperature, for measuring the circulation time of the right heart unit, i.e. from the antecubital veins to the pulmonary capillaries. The end-point is a facial grimace, cough or the perception of the ether smell by subject and investigator. Other volatile substances have since been suggested, the most satisfactory being paraldehyde. Paraldehyde, like ether, also offers an objective as well as a subjective end-point, but because 1.4 c.c. of the drug is employed it may cause transitory dizziness. The normal range of the arm-to-lung time with ether is from 3 to 8 seconds.

The circulation time of the left heart unit or from the pulmonary to the lingual capillaries may be estimated indirectly by subtracting the arm-to-lung time from the arm-to-tongue time. The normal range is from 4½ to 10 seconds. A direct method for measuring the circulation time from the pulmonary

capillaries to the carotid sinus determines the interval between inhalation of carbon dioxide and the first deep inspiration. The oximeter which registers a decrease in arterial oxygen saturation after one inhalation of 100 per cent nitrogen also permits direct measurement of the pulmonary to systemic capillary circulation time. The indirect and direct methods yield comparable readings in normal individuals, but wide variations in some pathologic conditions have been observed with the carbon dioxide method.

In heart failure, the arm-to-lung and arm-to-tongue times are useful in determining the segment of the circulation in which blood flow is retarded. Thus in left heart failure, Hitzig, King and Fishberg found that the arm-to-lung time was within the normal range whereas the lung-to-tongue time was often enormously increased. Similarly, in right heart failure secondary to left heart failure, both the arm-to-lung and lung-to-tongue times were increased, and the degree of increase paralleled the severity of the heart failure. On the other hand, in primary failure of the right heart secondary to extensive pulmonary disease (decompensated stage of cor pulmonale) or in constrictive pericarditis with predominant compression of the right heart, the arm-to-lung time was increased without increase of lung-to-tongue time.

Circulation times aid in evaluating the therapeutic response to digitalis and diuretics in congestive failure. The effect of surgical treatment of constrictive pericarditis and of arteriovenous fistula with heart failure has been dramatically demonstrated by means of studies of velocity of blood flow.

In thyroid disease the velocity of blood flow parallels, in general way, the base metabolic rate. In hyperthyroidism the circulation time is rapid but returns to the normal range following effective iodine therapy and thyroidectomy. Arm-to-tongue times ranging between 5½ and 8 seconds have been obtained in active Graves' disease. In myxedema the arm-to-tongue time is increased but returns to normal with thyroid therapy. Even in hyperthyroidism with universal heart failure the velocity of the blood may remain within the normal range.

In peripheral failure, the circulation time with ether and saccharin is either normal or slightly increased.

An application of the ether method has been reported by Benenson and Hitzig for the diagnosis of right to left shunt in congenital heart disease. In tetralogy of Fallot, for example, there is not only abbreviation of the arm-to-tongue time due to the short-circuiting of the injected substance into the left side of the heart when saccharin, decholin and calcium are employed, but unusual phenomena appear when ether is injected which serve as pathognomonic signs of right to left shunt. Ether travels in a gaseous state in the human body and is normally volatilized in the lungs. In the presence of pulmonary stenosis, the existing right to left shunt, whether due to septal defect or transposition of the vessels, permits short-circuiting of the vaporous ether and its dissemination in the systemic arterial circuit. This causes paresthetic phenomena in the skin of the head and face, namely, stinging and tingling sensations of a few seconds' duration. Depending upon the initial dose of ether and the amount shunted, this may even result in generalized paresthesias which extend in wave-like fashion to the distant parts of the body. In such congenital cardiac conditions, the arm-to-facial paresthesia time corresponds closely to the arm-to-lung and arm-to-tongue times. Similar ether-facial paresthesia times may be obtained in cases with patent interauricular septal defect and "idiopathic" dilatation of the pulmonary artery, and in conditions in which a common auricle exists. In the two latter instances the ether-smell time is equal to the ether-facial paresthesia time, but the arm-to-tongue time determined with calcium, decholin or saccharin remains within the normal physiologic range. Evidently, these substances are deviated in a quantity inadequate to produce a signal reaction although sufficient gaseous ether to cause paresthesias is shunted and disseminated through the systemic arterial capillaries. In the Lutembacher syndrome paresthesias may be obtained which indicate the presence of some cross current shunting of the vaporized ether due to the intra-auricular turbulence. Here, the ether-smell and ether-facial paresthesia times are equal although the arm-to-tongue time with decholin may actually be prolonged due to the existing mitral stenosis.

Illustrative cases	Ether Arm-to-facial paresthesia time	Ether Arm-to-lung time	Saccharin Arm-to-tongue time
Tetralogy of Fallot	4	7.5	4
Tetralogy of Fallot	6	7	7.5
Interauricular septal defect	8	8.5	17.5
Lutembacher syndrome	8.5	8.5	22

The most dramatic use of circulation times may be made in cases of severe asthma when the differential diagnosis between the bronchogenic and cardiac type is difficult without laboratory aids. During the asthmatic seizure of cardiac origin, the circulation time is invariably prolonged, but in bronchial asthma as in emphysema or in the presence of a single functioning lung the circulation time is either normal or accelerated. This rapid method of differentiation provided by determination of circulation time may help in the prompt institution of effective therapy.

In pernicious anemia and in non-carcinomatous secondary anemia, the velocity of blood flow through the lungs is inversely proportional to the hemoglobin content of the blood. The speed of blood flow in anemia parallels in a general way the findings in hyperthyroidism and fever, conditions also associated with an increased cardiac output. In polycythemia vera the circulation time is usually prolonged more as a result of the enormously increased volume of circulating blood rather than the greatly increased blood viscosity.

Circulation times have proved of value not only in the diagnosis of dominant retardation of blood flow in physiologic segments of the circulation and in the therapeutic guidance of circulatory insufficiency but also in the early recognition of conditions that mimic heart failure. With their aid the dyspnea of pulmonary origin, the anasarca of hypoproteinemia, the segmental systemic venous hypertension due to obstruction of either the superior or inferior vena cava and the hepatomegaly of amyloidosis, carcinoma or cirrhosis may be readily distinguished from analogous conditions of cardiac origin.

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